

PATENT COOPERATION TREATY

Pharmacia & Upjohn S.p.A.
PHEVETTI

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NOTIFICATION OF RECEIPT OF
RECORD COPY

(PCT Rule 24.2(a))

From the INTERNATIONAL BUREAU

To:

PHARMACIA & UPJOHN S.P.A.
Patent Dept.
Viale Pasteur, 10
I-20014 Nerviano
ITALIE

| | |
|--|---|
| Date of mailing (day/month/year) 27 May 1999 (27.05.99) | IMPORTANT NOTIFICATION |
| Applicant's or agent's file reference FC 844/5 | International application No. PCT/EP99/01822 |

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

PHARMACIA & UPJOHN S.P.A. (for all designated States except US)
COZZI, Paolo et al (for US)

International filing date : 17 March 1999 (17.03.99)
Priority date(s) claimed : 27 March 1998 (27.03.98)
Date of receipt of the record copy
by the International Bureau : 12 May 1999 (12.05.99)

List of designated Offices

AP : GH,GM,KE,LS,MW,SD,SZ,UG,ZW
EA : AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP : AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE
OA : BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG
National : AE,AL,AU,BA,BB,BG,BR,CA,CN,CU,CZ,EE,GD,GE,HR,HU,ID,IL,IN,IS,JP,KP,KR,LC,
LK,LR,LT,LV,MG,MK,MN,MX,NO,NZ,PL,RO,SG,SI,SK,SL,TR,TT,UA,US,UZ,VN,YU,ZA

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- ☒ time limits for entry into the national phase
☒ confirmation of precautionary designations
☐ requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

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| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland | Authorized officer: J. Leitao |
| Facsimile No. (41-22) 740.14.35 | Telephone No. (41-22) 338.83.38 |

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, provided that the election is made before the expiration of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. **It is the applicant's responsibility** to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1996 and 6 September 1997, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1996 and 6 September 1997, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity to furnish the priority document within a time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

PHARMACIA & UPJOHN S.P.A.
Patent Dept.
Viale Pasteur, 10
I-20014 Nerviano
ITALIE

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|--|--|
| Date of mailing (day/month/year) 27 May 1999 (27.05.99) | IMPORTANT NOTIFICATION |
| Applicant's or agent's file reference FC 844/5 | |
| International application No. PCT/EP99/01822 | |
| International publication date (day/month/year) Not yet published | |
| Applicant PHARMACIA & UPJOHN S.P.A. et al | International filing date (day/month/year) 17 March 1999 (17.03.99) Priority date (day/month/year) 27 March 1998 (27.03.98) |

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

| <u>Priority date</u> | <u>Priority application No.</u> | <u>Country or regional Office or PCT receiving Office</u> | <u>Date of receipt of priority document</u> |
|-------------------------|---------------------------------|---|---|
| 27 Marc 1998 (27.03.98) | 9806689.7 | GB | 12 May 1999 (12.05.99) |

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| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35 | Authorized officer J. Leitao Telephone No. (41-22) 338.83.38 |
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PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

PHARMACIA & UPJOHN S.P.A.
Patent Dept.
Viale Pasteur, 10
I-20014 Nerviano
ITALIE

Pharmacia & Upjohn S.p.A.
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| Date of mailing (day/month/year) 07 October 1999 (07.10.99) | | |
| Applicant's or agent's file reference FC 844/5 | | IMPORTANT NOTICE |
| International application No. PCT/EP99/01822 | International filing date (day/month/year) 17 March 1999 (17.03.99) | |
| Priority date (day/month/year) 27 March 1998 (27.03.98) | | |
| Applicant PHARMACIA & UPJOHN S.P.A. et al | | |

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
AU,CN,EP,IL,JP,KP,KR,US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
AE,AL,AP,BA,BB,BG,BR,CA,CU,CZ,EA,EE,GD,GE,HR,HU,ID,IN,IS,LC,LK,LR,LT,LV,MG,MK,MN, MX,NO,NZ,OA,PL,RO,SG,SI,SK,SL,TR,TT,UA,UZ,VN,YU,ZA

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 07 October 1999 (07.10.99) under No. WO 99/50265

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

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| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35 | Authorized officer J. Zahra Telephone No. (41-22) 338.83.38 |
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**NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF
THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES**

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|---|--|
| Date of mailing (day/month/year) 07 October 1999 (07.10.99) | IMPORTANT NOTICE |
| Applicant's representative's file reference FC 844/5 | International application No. PCT/EP99/01822 |

The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

PATENT COOPERATION TREATY

29 NOV 1999
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PCT

From the INTERNATIONAL BUREAU

To:

PHARMACIA & UPJOHN S.P.A.
Patent Dept.
Viale Pasteur, 10
I-20014 Nerviano
ITALIEINFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

| | | | |
|---|--|--|--|
| Date of mailing (day/month/year) 19 November 1999 (19.11.99) | | IMPORTANT INFORMATION | |
| Applicant's or agent's file reference FC 844/5 | | | |
| International application No. PCT/EP99/01822 | International filing date (day/month/year) 17 March 1999 (17.03.99) | Priority date (day/month/year) 27 March 1998 (27.03.98) | |
| Applicant PHARMACIA & UPJOHN S.P.A. et al | | | |

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

AP : GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW

EP : AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

National : AU, BG, BR, CA, CN, CZ, IL, JP, KP, KR, MN, NO, NZ, PL, RO, SK, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

OA : BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

National : AE, AL, BA, BB, CU, EE, GD, GE, HR, HU, ID, IN, IS, LC, LK, LR, LT, LV, MG, MK, MX, SG, SI, SL, TR, TT, UA, UZ, VN, YU, ZA

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

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| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35 | Authorized officer: F. Baechler Telephone No. (41-22) 338.83.38 |
|--|---|

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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| Applicant's or agent's file reference FC 844/5 | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/EP99/01822 | International filing date (day/month/year) 17/03/1999 | Priority date (day/month/year) 27/03/1998 |
| International Patent Classification (IPC) or national classification and IPC C07D403/14 | | |
| Applicant PHARMACIA & UPJOHN S.P.A. | | |

- This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
- This REPORT consists of a total of 6 sheets, including this cover sheet.
 - ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

- This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

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| Date of submission of the demand 21/10/1999 | Date of completion of this report 06.07.00 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016 | Authorized officer Paisdor, B Telephone No. +31 70 340 3764  |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/01822

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-47 as originally filed

Claims, No.:

1-11 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|------|-------------|
| Novelty (N) | Yes: | Claims 1-11 |
| | No: | Claims |
| Inventive step (IS) | Yes: | Claims |
| | No: | Claims 1-11 |
| Industrial applicability (IA) | Yes: | Claims 1-11 |
| | No: | Claims |

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP99/01822

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. Citations and Explanations

Reference is made to the following documents:

D1: WO,A,98 04524

D2: WO,A,96 05196

2.1 Novelty and Inventive Step (Articles 33(2) and 33(3) PCT)

2.1.1 Document D1, which is considered to represent the most relevant state of the art, discloses acryloyl substituted Distamycin derivatives, from which the subject-matter of claim 1 only differs in that the molecular Distamycin backbone only contains pyrrole as heterocyclic ring, whereas according to claim 1 of the present application, at least one of the heterocyclic rings has to be different from pyrrole. To show the distinguishing structural feature, example 1 of D1 (cf. page 21) and example 1 of the present application (cf. pages 20 -24) can be compared. The subject-matter of claim 1 is therefore novel (Article 33(2) PCT). The Distamycin A analogues of D1 are antitumor agents, just like the compounds of the present application.

2.1.2 The technical problem to be solved by this distinguishing structural feature may therefore be regarded as to provide further Distamycin derivatives as antitumor agents.

2.1.3 Providing the compounds of the present application as solutions of the aforementioned technical problem cannot be regarded as involving an inventive step in the present case, because another document of the prior art, D2, discloses a group of Distamycin A derivatives as antitumor agents wherein one heterocyclic group of the polyheterocyclic chain of the Distamycin backbone is different from pyrrole, i.e. it is for

instance a pyrazole ring (cf. example 1 of D2, pages 36 - 39). The formyl group of the Distamycin portion is not replaced by an acryloyl moiety, as it is the case in the present application, but by a group R^1R^2N-A- . In D2, at least one of the heterocyclic rings within the polyheterocyclic chain is other than pyrrole; in all examples of D1 the group B (corresponding to group B of claim 1 of the present application) is an unsubstituted amidine group being excluded from the scope of the present claim 1 by means of the proviso a), but in D1 the unsubstituted amidine group is included as an alternative of group B. Since it is known from D2, to provide Distamycin A analogues with pyrrole heterocycles in the polyheterocyclic chain replaced by at least one different heterocyclic group as solutions of the technical problem underlying the present application, a person skilled in the art **would** have included the distinguishing structural feature of replacing a pyrrole ring by a pyrazole ring in order to solve the technical problem posed.

2.1.4 An unexpected property or effect having its origin in the above defined distinguishing structural feature of exchanging one pyrrole moiety by another heterocyclic moiety has to be shown in order to justify an inventive step of the claimed Distamycin A analogues. At present, there is no evidence for any such unexpected properties on file, and consequently, the independent claim 1 lacks inventive step in the sense of Article 33(3) PCT.

2.1.5 The dependent claims 2 - 5, the process claims 6 and 7, and the claims 8 - 11 pertaining to pharmaceutical compositions containing compounds of claim 1 or their medical applications, to not contain additional technical features being relevant for the assessment of inventive step. These claims, although they represent novel subject-matter in the sense of Article 33(2) PCT, nevertheless **do not meet** the requirements of Article 33(3) PCT and lack inventive step.

2.2 Industrial Applicability (Article 33(4) PCT)

The compounds claimed in the present application can be used for the preparation of pharmaceutical compositions and for the preparation of medicaments containing the claimed compounds.

Re Item VII

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/01822

Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor is this document identified therein.
2. The units of pressure employed on pages 33 and 43 (psi) is not additionally expressed in terms of the units stipulated by Rule 10.1 (a) PCT.

Re Item VIII

Certain observations on the international application

Claim 5 comprises all the features of claim 1 and is therefore not appropriately formulated as a claim dependent on the latter (Rule 6.4 PCT).